CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for: 074834

Trade Name : ACYCLOVIR TABLETS 400MG AND 800MG

Generic Name: Acyclovir Tablets 400mg and 800mg

Sponsor : ESI Lederle, Inc.

Approval Date: April 24, 1997

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APPLICATION 074834

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074834

APPROVAL LETTERS

ANDA 74-834

APR 24 1997

ESI Lederle, Inc.
Attention: Nicholas C. Tantillo
401 North Middletown Road
Pearl River, NY 10965-1299

Dear Sir:

This is in reference to your abbreviated new drug application dated January 12, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Tablets, 400 mg and 800 mg.

Reference is also made to your amendments dated September 13, and November 11, 1996, March 6, and April 10, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Acyclovir Tablets, 400 mg and 800 mg to be bioequivalent and, therefore therapeutically equivalent, to the listed drug (Zovirax® Tablets, 400 mg and 800 mg respectively, of Glaxo Wellcome Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in these abbreviated applications require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for these abbreviated applications are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of these drugs.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign, at the time of their initial use, be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253.

Sincerely yours,

for/ 4/24/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074834

FINAL PRINTED LABELING

Usual Dosage: See package circular for complete prescribing information.

ESI Lederle Inc.
Philadelphia, PA 19101 U3163-01-1

NDC 59911-3163-1

ESI LEDERLE

Acyclovir Tablets

400 mg

100 Tablets

Caution: Federal law prohibits dispensing without prescription.

Store between 15°-25°C (59°-77°F).
Protect from light and moisture.
Dispense in a tight, light-resistant container with a child-resistant closure.
This is a bulk container not intended for household use.

SAMPLE 80% MAGNIFICATION
N 3 00000-0000-0

Control No.:

Exp. Date:

NDC 59911-3163-2

ESI LEDERLE

Acyclovir Tablets

400 mg

1000 Tablets

Caution: Federal law prohibits dispensing without prescription.

Control No.:

Exp. Date:

Usual Dosage: See package circular for complete prescribing information.

Store between 15°-25°C (59°-77°F).

Protect from light and moisture.

Dispense in a tight, light-resistant container with a child-resistant closure.

This is a bulk container not intended for household use.

ESI Lederle Inc.
Philadelphia, PA 19101 U3163-02-1

SAMPLE 100% MAGNIFICATION
N 3 00000-0000-0

NDC 59911-3164-2

ESI LEDERLE

Acyclovir Tablets

800 mg

500 Tablets

Caution: Federal law prohibits dispensing without prescription.

Control No.:

Exp. Date:

Usual Dosage: See package circular for complete prescribing information.

Store between 15°-25°C (59°-77°F).

Protect from light and moisture.

Dispense in a tight, light-resistant container with a child-resistant closure.

This is a bulk container not intended for household use.

ESI Lederle Inc.
Philadelphia, PA 19101 U3164-02-

SAMPLE 100% MAGNIFICATION
N 3 00000-0000-0

NDC 59911-3164-4

ESI LEDERLE

Acyclovir Tablets

800 mg

100 Tablets

Caution: Federal law prohibits dispensing without prescription.

Usual Dosage: See package circular for complete prescribing information.

Store between 15°-25°C (59°-77°F).
Protect from light and moisture.
Dispense in a tight, light-resistant container with a child-resistant closure.

SAMPLE 100% MAGNIFICATION

N 3 00000-0000-0

Control No.:

Exp. Date:

ESI Lederle Inc.
Philadelphia, PA 19101

U3164-04-1

NDC 59911-3163-5

ESI LEDERLE

Acyclovir Tablets

400 mg

500 Tablets

Caution: Federal law prohibits dispensing without prescription.

Usual Dosage: See package circular for complete prescribing information.

Store between 15°-25°C (59°-77°F).

Protect from light and moisture.

Dispense in a tight, light-resistant container with a child-resistant closure.

This is a bulk container not intended for household use.

ESI Lederle Inc.
Philadelphia, PA 19101

U3163-05-

SAMPLE 100% MAGNIFICATION

N 3 00000-0000-0

Control No.:

Exp. Date:

Acyclovir Tablets
CI 4643

LEDERLE™

2 4 1997

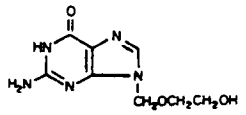
Acyclovir Tablets

DESCRIPTION

Acyclovir is an antiviral drug. Acyclovir tablets are formulated for oral administration.

Each tablet of acyclovir contains 400 mg or 800 mg of acyclovir and the following inactive ingredients: magnesium stearate, microcrystalline cellulose, povidone, silicon dioxide, and sodium starch glycolate.

The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6*H*-purin-6-one. It has the following structural formula:



$C_8H_{11}N_5O_3$ M.W. 225.21

Acyclovir is a white to off-white, crystalline powder with a molecular weight of 225.21, and a maximum solubility in water of 2.5 mg/mL at 37°C.

CLINICAL PHARMACOLOGY

Mechanism of Antiviral Effects

Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against human herpes viruses including herpes simplex types 1 (HSV-1) and 2 (HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV). In cell culture, acyclovir has the highest antiviral activity against HSV-1, followed in decreasing order of potency against HSV-2, VZV, EBV, and CMV.[1]

The inhibitory activity of acyclovir for HSV-1, HSV-2, VZV, and EBV is highly selective. The enzyme thymidine kinase (TK) of normal uninfected cells does not effectively use acyclovir as a substrate. However, TK encoded by HSV, VZV, and EBV[2] converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes.[3] Acyclovir triphosphate interferes with herpes simplex virus DNA polymerase and inhibits viral DNA replication. Acyclovir triphosphate also inhibits cellular α-DNA polymerase, but to a lesser degree. *In vitro*, acyclovir triphosphate can be incorporated into growing chains of DNA by viral DNA polymerase and to a much smaller extent by cellular α-DNA polymerase.[4] When incorporation occurs, the DNA chain is terminated.[3,5] Acyclovir is preferentially taken up and selectively converted to the active triphosphate form by herpesvirus-infected cells. Thus, acyclovir is much less toxic *in vitro* for normal uninfected cells because: 1) less is taken up; 2) less is converted to the active form; 3) cellular α-DNA polymerase is less sensitive to the effects of the active form. The mode of acyclovir phosphorylation in cytomegalovirus-infected cells is not clearly established, but may involve virally induced cell kinases or an unidentified viral enzyme. Acyclovir is not efficiently activated in cytomegalovirus-infected cells, which may account for the reduced susceptibility of cytomegalovirus to acyclovir *in vitro*.

Microbiology

The quantitative relationship between the *in vitro* susceptibility of herpes simplex and varicella-zoster viruses to acyclovir and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (ID_{50}), vary greatly depending upon the particular assay used,[7] the cell type employed,[8] and the laboratory performing the test.[1] The ID_{50} of acyclovir against HSV-1 isolates may range from 0.02 mcg/mL (plaque reduction in Vero cells) to 5.9 to 13.5 mcg/mL (plaque reduction in green monkey kidney [GMK] cells).[1] The ID_{50} against HSV-2 ranges from 0.01 mcg/mL to 9.9 mcg/mL (plaque reduction in Vero and GMK cells, respectively)[1].

Using a dye-uptake method in Vero cells,[9] which gives ID_{50} values approximately 5- to 10-fold higher than plaque reduction assays, 1417 HSV isolates (553 HSV-1 and 864 HSV-2) from approximately 500 patients were examined over a 5-year period.[10] These assays found that 90% of HSV-1 isolates were sensitive to ≤ 0.9 mcg/mL acyclovir and 50% of all isolates were sensitive to ≤ 0.2 mcg/mL acyclovir. For HSV-2 isolates, 90% were sensitive to ≤ 2.2 mcg/mL and 50% of all isolates were sensitive to ≤ 0.7 mcg/mL of acyclovir. Isolates with significantly diminished sensitivity were found in 44 patients. It must be emphasized that neither the patients nor the isolates were randomly selected and, therefore, do not represent the general population.

Most of the less sensitive HSV clinical isolates have been relatively deficient in the viral TK.[11-19] Strains with alterations in viral TK[20] or viral DNA polymerase[21] have also been reported. Prolonged exposure to low concentrations (0.1 mcg/mL) of acyclovir in cell culture has resulted in the emergence of a variety of acyclovir-resistant strains.[22]

The ID_{50} against VZV ranges from 0.17 to 1.53 mcg/mL (yield reduction, human foreskin fibroblasts) to 1.85 to 3.98 mcg/mL (foci reduction, human embryo fibroblasts [HEF]). Reproduction of EBV genome is suppressed by 50% in superinfected Raji cells or P3HR-1 lymphoblastoid cells by 1.5 mcg/mL acyclovir. CMV is relatively resistant to acyclovir with ID_{50} values ranging from 2.3 to 17.6 mcg/mL (plaque reduction, HEF cells) to 1.82 to 56.8 mcg/mL (DNA hybridization, HEF cells). The latent state of the genome of any of the human herpesviruses is not known to be sensitive to acyclovir.[1]

Pharmacokinetics

The pharmacokinetics of acyclovir after oral administration have been evaluated in 6 clinical studies involving 110 adult patients. In one uncontrolled study of 35 immunocompromised patients with herpes simplex or varicella-zoster infection, acyclovir capsules were administered in doses of 200 to 1000 mg every 4 hours, 6 times daily for 5 days, and steady-state plasma levels were reached by the second day of dosing. Mean steady-state peak and trough concentrations following the final 200 mg dose were 0.49 mcg/mL (0.47 to 0.54 mcg/mL) and 0.31 mcg/mL (0.18 to 0.41 mcg/mL), respectively, and following the final 800 mg dose were 2.8 mcg/mL (2.3 to 3.1 mcg/mL) and 1.8 mcg/mL (1.3 to 2.5 mcg/mL), respectively. In another uncontrolled study of 20 younger immunocompetent patients with recurrent genital herpes simplex infections, acyclovir capsules were administered in doses of 800 mg every 6 hours, 4 times daily for 5 days; the mean steady-state peak and trough concentrations were 1.4 mcg/mL (0.66 to 1.8 mcg/mL) and 0.55 mcg/mL (0.14 to 1.1 mcg/mL), respectively.

In general, the pharmacokinetics of acyclovir in children is similar to adults. Mean half-life after oral doses of 300 mg/m² and 600 mg/m², in children ages 7 months to 7 years, was 2.6 hours (range 1.59 to 3.74 hours).

In a reported single-dose bioavailability/bioequivalence study in 24 volunteers, one acyclovir 800 mg tablet was demonstrated to be bioequivalent to four acyclovir 200 mg capsules.

In a multiple-dose crossover study where 23 volunteers received acyclovir as one 200 mg capsule, one 400 mg tablet, and one 800 mg tablet 6 times daily, absorption decreased with increasing dose and the estimated bioavailabilities of acyclovir were 20%, 15%, and 10%, respectively. The decrease in bioavailability is believed to be a function of the dose and not the dosage form. It was demonstrated that acyclovir is not dose proportional over the dosing range 200 mg to 800 mg. In this study, steady-state peak and trough concentrations of acyclovir were 0.83 and 0.46 mcg/mL, 1.21 and 0.63 mcg/mL, and 1.61 and 0.83 mcg/mL for the 200, 400, and 800 mg dosage regimens, respectively.

In another study, the influence of food on the absorption of acyclovir was not apparent.

Following oral administration, the mean plasma half-life of acyclovir in volunteers and patients with normal renal function ranged from 2.5 to 3.3 hours. The mean renal excretion of unchanged drug accounts for 14.4% (8.6% to 19.8%) of the orally administered dose. The only urinary metabolite (identified by high performance liquid chromatography) is 9-[(carboxymethoxy)methyl]guanine. The half-life and total body clearance of acyclovir are dependent on renal function. A dosage adjustment is recommended for patients with reduced renal function (see **DOSAGE AND ADMINISTRATION**).

Orally administered acyclovir in children less than 2 years of age has not yet been fully studied.

INDICATIONS AND USAGE

Acyclovir tablets are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

Acyclovir tablets are indicated for the acute treatment of herpes zoster (shingles) and chickenpox (varicella).

Genital Herpes Infections

The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement. These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy. The physical, emotional, and psychosocial difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs. Thus, orally administered acyclovir is not appropriate in treating all genital herpes infections. The following guidelines may be useful in weighing the benefit/risk considerations in specific disease categories:

First Episodes (primary and nonprimary infections—commonly known as initial genital herpes):

Double-blind, placebo-controlled studies[23,24,26] have demonstrated that orally administered acyclovir significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing. The duration of pain and new lesion formation was decreased in some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to herpes simplex virus may influence the degree of benefit from therapy. Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention, or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous acyclovir.

Recurrent Episodes:

Double-blind, placebo-controlled studies[6,29-32] in patients with frequent recurrences (6 or more episodes per year) have shown that orally administered acyclovir given daily for 4 months to 3 years prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients.

In a study of 283 patients who received acyclovir 400 mg (two 200 mg capsules) twice daily for 3 years, 45%, 52%, and 63% of patients remained free of recurrences in the first, second, and third years, respectively. Serial analyses of the 3-month recurrence rates for the 283 patients showed that 71% to 87% were recurrence-free in each quarter, indicating that the effects are consistent over time.

The frequency and severity of episodes of untreated genital herpes may change over time. After one year of therapy, the frequency and severity of the patient's genital herpes infection should be reevaluated to assess the need for continuation of acyclovir therapy. Reevaluation will usually require a trial off acyclovir to assess the need for reinstitution of suppressive therapy. Some patients, such as those with very frequent or severe episodes before treatment, may warrant uninterrupted suppression for more than a year.

Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects. In general, orally administered acyclovir should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the relevance to humans of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given high parenteral doses of acyclovir for short periods (see **PRECAUTIONS: Carcinogenesis, Mutagenesis,**

Impairment of Fertility) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease. Thus, this regimen should be considered only for appropriate patients with annual reevaluation.

Limited studies[31,32] have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences.

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy. Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions.

Herpes Zoster Infections

In a double-blind, placebo-controlled study of 187 normal patients with localized cutaneous zoster infection (93 randomized to acyclovir and 94 to placebo), acyclovir (800 mg 5 times daily for 10 days) shortened the times to lesion scabbing, healing, and complete cessation of pain, and reduced the duration of viral shedding and the duration of new lesion formation.[33]

In a similar double-blind, placebo-controlled study in 83 normal patients with herpes zoster (40 randomized to acyclovir and 43 to placebo), acyclovir (800 mg 5 times daily for 7 days) shortened the times to complete lesion scabbing, healing, and cessation of pain, reduced the duration of new lesion formation, and reduced the prevalence of localized zoster-associated neurologic symptoms (paresthesia, dysesthesia, or hyperesthesia).[34]

Chickenpox

In a double-blind, placebo-controlled efficacy study in 110 normal patients, ages 5 to 16 years, who presented **within 24 hours** of the onset of a typical chickenpox rash, acyclovir was administered orally 4 times daily for 5 to 7 days at doses of 10, 15, or 20 mg/kg depending on the age group. Treatment with acyclovir reduced the maximum number of lesions (336 vs. greater than 500; lesions beyond 500 were not counted). Treatment with acyclovir also shortened the mean time to 50% healing (7.1 days vs. 8.7 days), reduced the number of vesicular lesions by the second day of treatment (49 vs. 113), and decreased the proportion of patients with fever (temperature greater than 100°F) by the second day (19% vs. 57%). Treatment with acyclovir did not affect the antibody response to varicella-zoster virus measured 1 month and 1 year following the treatment.[35]

In two concurrent double-blind, placebo-controlled studies, a total of 883 normal patients, ages 2 to 18 years, were enrolled **within 24 hours** of the onset of a typical chickenpox rash, and acyclovir was administered at 20 mg/kg orally up to 800 mg 4 times daily for 5 days. In the larger study of 815 children ages 2 to 12 years, treatment with acyclovir reduced the median maximum number of lesions (277 vs. 386), reduced the median number of vesicular lesions by the second day of treatment (26 vs. 40), and reduced the proportion of patients with moderate to severe itching by the third day of treatment (15% vs. 34%).[36] In addition, in both studies (883 patients, ages 2 to 18 years), treatment with acyclovir also decreased the proportion of patients with fever (temperature greater than 100°F), anorexia, and lethargy by the second day of treatment, and decreased the mean number of residual lesions on Day 28.[36,37] There were no substantial differences in VZV-specific humoral or cellular immune responses measured at one month following treatment in patients receiving acyclovir compared to patients receiving placebo.[36]

Diagnosis

Diagnosis is confirmed by virus isolation. Accelerated viral culture assays or immunocytology allow more rapid diagnosis than standard viral culture. For patients with initial episodes of genital herpes, appropriate examinations should be performed to rule out other sexually transmitted diseases. While cutaneous lesions associated with herpes simplex and varicella-zoster infections are often characteristic, the finding of multinucleated giant cells in smears prepared from lesion exudate or scrapings may provide additional support to the clinical diagnosis.[39]

Multinucleated giant cells in smears do not distinguish varicella-zoster from herpes simplex infections.

CONTRAINDICATIONS

Acyclovir tablets are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulation.

WARNINGS

Acyclovir tablets are intended for oral ingestion only.

PRECAUTIONS

General

Acyclovir has caused decreased spermatogenesis at high parenteral doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility**). The recommended dosage should not be exceeded (see **DOSAGE AND ADMINISTRATION**).

Exposure of herpes simplex and varicella-zoster isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in humans must be borne in mind when treating patients. The relationship between the *in vitro* sensitivity of herpes simplex or varicella-zoster virus to acyclovir and clinical response to therapy has yet to be established (see **CLINICAL PHARMACOLOGY: Microbiology**).

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

Caution should be exercised when administering acyclovir to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction.

Information for Patients

Patients are instructed to consult with their physician if they experience severe or troublesome adverse reactions, they become pregnant or intend to become pregnant, they intend to breastfeed while taking orally administered acyclovir, or they have any other questions.

Genital Herpes Infections: Genital herpes is a sexually transmitted disease and patients should avoid intercourse when visible lesions are present because

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of the risk of infecting intimate partners. Acyclovir tablets are for oral ingestion only. Medication should not be shared with others. The prescribed dosage should not be exceeded. Acyclovir does not eliminate latent viruses. Patients are instructed to consult with their physician if they do not receive sufficient relief in the frequency and severity of their genital herpes recurrences.

There are still unanswered questions concerning reproductive/gonadal toxicity and mutagenesis; long-term studies are continuing. Decreased sperm production has been seen at high doses in some animals; a placebo-controlled clinical study using 400 mg or 1000 mg of acyclovir per day for six months in humans did not show similar findings.[40] Chromosomal breaks were seen *in vitro* after brief exposure to high concentrations. Some other currently marketed medications also cause chromosomal breaks, and the significance of this finding is unknown. A placebo-controlled clinical study using 800 mg of acyclovir per day for one year in humans did not show any abnormalities in structure or number of chromosomes.[28]

Herpes Zoster Infections: Adults age 50 or older tend to have more severe shingles, and treatment with acyclovir showed more significant benefit for older patients. Treatment was begun within 72 hours of rash onset in these studies, and was more useful if started within the first 48 hours.

Chickenpox: Although chickenpox in otherwise healthy children is usually a self-limited disease of mild to moderate severity, adolescents and adults tend to have more severe disease.

Treatment was initiated within 24 hours of the typical chickenpox rash in the controlled studies, and there is no information regarding the effects of treatment begun later in the disease course. It is unknown whether the treatment of chickenpox in childhood has any effect on long-term immunity. However, there is no evidence to indicate that treatment of chickenpox with acyclovir would have any effect on either decreasing or increasing the incidence or severity of subsequent recurrences of herpes zoster (shingles) later in life. Intravenous acyclovir is indicated for the treatment of varicella-zoster infections in immunocompromised patients.

Drug Interactions

Coadministration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.[41] The clinical effects of this combination have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The data presented below include references to peak steady-state plasma acyclovir concentrations observed in humans treated with 800 mg given orally 6 times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally 6 times a day (dosing appropriate for treatment of genital herpes). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. At 450 mg/kg/day, plasma concentrations were 3 to 6 times human levels in the mouse bioassay and 1 to 2 times human levels in the rat bioassay.

Acyclovir was tested in two *in vitro* cell transformation assays. Positive results were observed at the highest concentration tested (31 to 63 times human levels) in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative (40 to 80 times human levels) in the other, possibly less sensitive, transformation assay.

In acute cytogenetic studies, there was an increase, though not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of acyclovir (100 mg/kg) in rats (62 to 125 times human levels) but not in Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters (380 to 760 times human levels). In addition, no activity was found after 5 days dosing in a dominant lethal study in mice (36 to 73 times human levels). In all 4 microbial assays, no evidence of mutagenicity was observed. Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells *in vitro*. In human lymphocytes, a positive response for chromosomal damage was seen at concentrations 150 to 300 times the acyclovir plasma levels achieved in humans. At one locus in mouse lymphoma cells, mutagenicity was observed at concentrations 250 to 500 times human plasma levels. Results in the other five mammalian cell loci follow: at 3 loci in a Chinese hamster ovary cell line, the results were inconclusive at concentrations at least 1850 times human levels; at 2 other loci in mouse lymphoma cells, no evidence of mutagenicity was observed at concentrations at least 1500 times human levels.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day p.o.) or in rats (25 mg/kg/day s.c.). In the mouse study, plasma levels were 9 to 18 times human levels, while in the rat study they were 8 to 15 times human levels. At a higher dose in the rat (50 mg/kg/day s.c.), there was a statistically significant increase in postimplantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day (16 to 31 times human levels). No effect upon implantation efficiency was observed when the same dose was administered intravenously (53 to 106 times human levels). In a rat peri- and postnatal study at 50 mg/kg/day s.c. (11 to 22 times human levels), there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites, and live fetuses in the F1 generation. Although not statistically significant, there was also a dose-related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a

corresponding decrease in litter size (plasma levels were not measured). However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits (53 to 106 times human levels), no drug-related reproductive effects were observed.

Intraperitoneal doses of 80 or 320 mg/kg/day acyclovir given to rats for 6 and 1 months, respectively, caused testicular atrophy. Plasma levels were not measured in the 1-month study and were 24 to 48 times human levels in the 6-month study. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. At 100 mg/kg/day plasma levels were 47 to 94 times human levels, while at 200 mg/kg/day they were 159 to 317 times human levels. No testicular abnormalities were seen in dogs given 50 mg/kg/day i.v. for one month (21 to 41 times human levels) and in dogs given 60 mg/kg/day orally for one year (6 to 12 times human levels).

Pregnancy

Teratogenic Effects: Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day p.o.), rabbit (50 mg/kg/day s.c. and i.v.), or in standard tests in the rat (50 mg/kg/day s.c.). These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels. In a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity.[42] In this test, rats were given 3 s.c. doses of 100 mg/kg acyclovir on gestation Day 10, resulting in plasma levels 63 and 125 times human levels. There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

Nursing Mothers

Acyclovir concentrations have been documented in breast milk in two women following oral administration of acyclovir and ranged from 0.6 to 4.1 times corresponding plasma levels.[43,44] These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Caution should be exercised when acyclovir is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients less than 2 years of age have not been adequately studied.

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ADVERSE REACTIONS

Herpes Simplex

Short-Term Administration: The most frequent adverse events reported during clinical trials of treatment of genital herpes with orally administered acyclovir were nausea and/or vomiting in 8 of 298 patient treatments (2.7%) and headache in 2 of 298 (0.6%). Nausea and/or vomiting occurred in 2 of 287 (0.7%) patients who received placebo.

Less frequent adverse events, each of which occurred in 1 of 298 patient treatments with orally administered acyclovir (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste, and sore throat.

Long-Term Administration: The most frequent adverse events reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 patients treated with acyclovir were: nausea (4.8%), diarrhea (2.4%), headache (1.9%), and rash (1.7%). The 589 control patients receiving intermittent treatment of recurrences with acyclovir for one year reported diarrhea (2.7%), nausea (2.4%), headache (2.2%), and rash (1.5%).

The most frequent adverse events reported during the second year by 390 patients who elected to continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 years were headache (1.5%), rash (1.3%), and paresthesia (0.8%). Adverse events reported by 329 patients during the third year included asthenia (1.2%), paresthesia (1.2%), and headache (0.9%).

Herpes Zoster

The most frequent adverse events reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral acyclovir 5 times daily for 7 to 10 days in 323 patients were: malaise (11.5%), nausea (8.0%), headache (5.9%), vomiting (2.5%), diarrhea (1.5%), and constipation (0.9%). The 323 placebo recipients reported malaise (11.1%), nausea (11.5%), headache (11.1%), vomiting (2.5%), diarrhea (0.3%), and constipation (2.4%).

Chickenpox

The most frequent adverse events reported during three clinical trials of treatment of chickenpox with oral acyclovir in 495 patients were: diarrhea (3.2%), abdominal pain (0.6%), rash (0.6%), vomiting (0.6%), and flatulence (0.4%). The 498 patients receiving placebo reported: diarrhea (2.2%), flatulence (0.8%), and insomnia (0.4%).

Observed During Clinical Practice

Based on clinical practice experience in patients treated with oral acyclovir in the U.S., spontaneously reported adverse events are uncommon. Data are insufficient to support an estimate of their incidence or to establish causation. These events may also occur as part of the underlying disease process. Voluntary reports of adverse events which have been received since market introduction include:

General: fever, headache, pain, peripheral edema, and rarely, anaphylaxis

Nervous: confusion, dizziness, hallucinations, paresthesia, seizure, somnolence (These symptoms may be marked, particularly in older adults.)

Digestive: diarrhea, elevated liver function tests, gastrointestinal distress, nausea

Hemic and Lymphatic: leukopenia, lymphadenopathy

Musculoskeletal: myalgia

Skin: alopecia, pruritus, rash, urticaria

Special Senses: visual abnormalities

Urogenital: elevated creatinine

OVERDOSAGE

Patients have ingested intentional overdoses of up to 100 capsules (20 g) of acyclovir, with no unexpected adverse effects.

Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) in the intratubular fluid is exceeded. Renal lesions considered to be related to obstruction of renal tubules by precipitated drug crystals occurred in the following species: rats treated with i.v. and i.p. doses of 20 mg/kg/day for 21 and 31 days, respectively, and at s.c. doses of 100 mg/kg/day for 10 days; rabbits at s.c. and i.v. doses of 50 mg/kg/day for 13 days; and dogs at i.v. doses of 100 mg/kg/day for 31 days. A 6-hour hemodialysis results in a 60% decrease in plasma acyclovir concentration. Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see **DOSAGE AND ADMINISTRATION**).

DOSAGE AND ADMINISTRATION

Treatment of Initial Genital Herpes

200 mg every 4 hours, 5 times daily for 10 days.

Chronic Suppressive Therapy for Recurrent Disease

400 mg (one 400 mg tablet) 2 times a day for up to 12 months, followed by reevaluation. See **INDICATIONS AND USAGE** and **PRECAUTIONS** for considerations on continuation of suppressive therapy beyond 12 months. Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily.

Intermittent Therapy

200 mg every 4 hours, 5 times daily for 5 days. Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Acute Treatment of Herpes Zoster

800 mg (two 400 mg tablets or one 800 mg tablet) every 4 hours orally, 5 times daily for 7 to 10 days.

Treatment of Chickenpox

Children (2 years of age and older): 20 mg/kg per dose orally four times daily (80 mg/kg/day) for 5 days. Children over 40 kg should receive the adult dose for chickenpox.

Adults and children over 40 kg: 800 mg four times daily for 5 days.

Therapy should be initiated at the earliest sign or symptom of chickenpox to derive the maximal benefits of therapy.

Patients With Acute or Chronic Renal Impairment

Comprehensive pharmacokinetic studies have been completed following intravenous acyclovir infusions in patients with renal impairment. Based on these studies, dosage adjustments are recommended in the following chart for genital herpes and herpes zoster indications:

Normal Dosage Regimen	Creatinine Clearance (mL/min/1.73m²)	Adjusted Dosage Regimen: Dose (mg)	Adjusted Dosage Regimen: Dosing Interval
200 mg every 4 hours	>10	200	every 4 hours, 5x daily
	0-10	200	every 12 hours
400 mg every 12 hours	>10	400	every 12 hours
	0-10	200	every 12 hours
800 mg every 4 hours	>25	800	every 4 hours, 5x daily
	10-25	800	every 8 hours
	0-10	800	every 12 hours

Hemodialysis

For patients who require hemodialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a 6-hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.[45,46]

Peritoneal Dialysis

No supplemental dose appears to be necessary after adjustment of the dosing interval.[47,48]

HOW SUPPLIED

Acyclovir tablets for oral administration are supplied as follows:

400 mg - round, white, unscored tablet engraved "511" on one side and "A75" on the other side, available as:

NDC 59911-3163-1 - Bottle of 100
NDC 59911-3163-4 - Bottle of 100 with CRC
NDC 59911-3163-5 - Bottle of 500
NDC 59911-3163-2 - Bottle of 1000

800 mg - oval, white, unscored tablet engraved "511" on one side and "A77" on the other side, available as:

NDC 59911-3164-1 - Bottle of 100
NDC 59911-3164-4 - Bottle of 100 with CRC
NDC 59911-3164-2 - Bottle of 500

Caution: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container with a child-resistant closure Protect from light and moisture.

Store between 15°-25°C (59°-77°F).

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ESI Lederle Inc.
Philadelphia, PA 19101
CI 4643 Issued February 27, 1997 Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074834

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. #3

2. AND #74-834

3. NAME AND ADDRESS OF APPLICANT
401 North Middle town Road
Attention to: Nicholas C. Tantillo
Pearl River, New York 10965-1299

4. LEGAL BASIS FOR SUBMISSION
This application is based is Zovirax® Tablets, 400 mg and 800 mg manufactured by Glaxo Wellcome.

A new drug application for acyclovir Tablets, 400 mg and 800 mg submitted by ESI Lederle Inc.
Patent expiration date for Acyclovir Tablet is April 22, 1997 (US Patent 4,199,574). The firm request that approval of this application be made effective on April 22, 1997.

According to information published in "Approved Drug Products with Therapeutic Equivalents Evaluations", 15th Edition, the listed reference drug is no longer entitled to a period of market exclusivity under section 505 (j)(4)(D) of the Food, Drugs and Cosmetic Act. The most recent period of market exclusivity expired on February 26, 1995.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Acyclovir Tablet

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
January 12, 1996: Original submission
January 31, 1996: New correspondence
September 13, 1996: Amendment
November 11,1996: Bio. correspondence
April 10, 1997: Fax Amendment

FDA: February 16, 1996: Acknowledge
January 12,1996: Deficiency letter
April 8, 1997: Fax. deficiency letter

10. PHARMACOLOGICAL CATEGORY
Antiviral

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

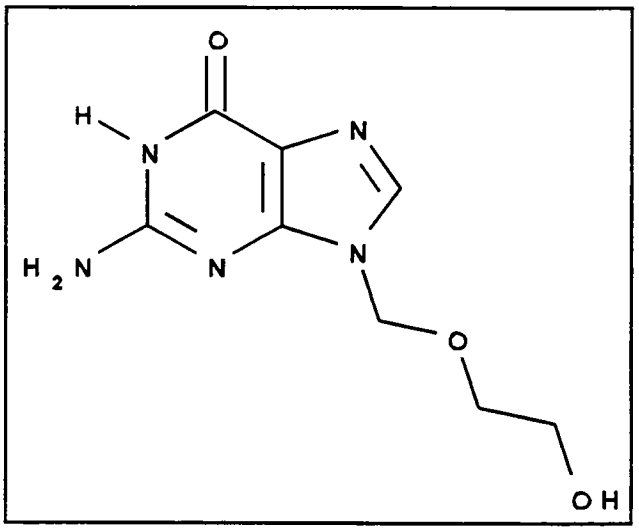
13. DOSAGE FORM
Oral Tablet

14. POTENCY
400 mg and 800 mg

15. CHEMICAL NAME AND STRUCTURE

Acyclovir USP

$C_8H_{11}N_5O_3$; M.W. = 225.21



9-[(2-Hydroxyethoxy)methyl]guanine. CAS [59277-89-3]

16. RECORDS AND REPORTS
Letter of authorization for reference to the , Debarment certification and Field copy certification are provided in section XXI on pages 674-679.

17. COMMENTS
The following deficiencies are found:

-Pending for Bioequivalency status

18. CONCLUSIONS AND RECOMMENDATIONS
The application can be approved. The approvable letter will be issued.

19. REVIEWER: DATE COMPLETED:

Sema Basaran, Ph.D. 4-15-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074834

BIOEQUIVALENCE REVIEW(S)

ANDA 74-834

APR 28 1997

ESI Lederle
Attention: Nicholas C. Tantillo
401 Middletown Road
Pearl River NY 10965-1299

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Acyclovir Tablets 400 mg and 800 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus II (Paddle) at 50 rpm. The test product should meet the following specification:

   Not less than of the labeled amount of acyclovir in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

for Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APR 23 1997

Acyclovir Tablets
400 MG, 800 MG
ANDA #74-834
Reviewer: S.P. Shrivastava
WP #74834o.n96

ESI-Lederle, Inc.
Pearl River, NY
Submitted:
November 11, 1996

REVIEW OF DEFICIENCY RESPONSE

I. BACKGROUND

The firm had submitted two *in vivo* bioequivalence studies comparing its 800 mg strength Acyclovir Tablets to Burroughs-Wellcome's 800 mg strength Zovirax^{R} Tablets, under fasting and non-fasting conditions. The firm had also submitted *in vitro* dissolution data for review. The review was completed and deficiencies were cited (Re: review by Shrivastava, 9/27/96). In this communication the firm has responded to the deficiencies.

II. RESPONSE TO DEFICIENCIES

Deficiency 1. *The product does not meet the 90% CI criteria for LC_{max} PK parameter. The LC_{max} of test product is 15% greater than the reference product.*

Response:

Results of single-dose fasting study (from revised data)

1. **Blood/Plasma Drug Concentration:** Since Subject #23 was dosed one week later, the subject was excluded from the analyses. The mean plasma concentration data are given in Table 1, and profiles are shown in Attachment 2, respectively.

2. **Pharmacokinetic Parameters**: Mean PK parameters and statistical analysis are given in Tables 2-3.

- The 90% CI for LAUCs are within 80-125% as required (Tables 2, 3).

Conclusion: Firm's response and explanation to the deficiency is acceptable. ANOVA on new data set on the diskette was run. The 90% CIs for PK parameters are within the required limits (Table 3). The *in vivo* fasting study is acceptable.

TABLE 1. MEAN PLASMA ACYCLOVIR LEVELS FOR TEST AND REFERENCE PRODUCTS (WITHOUT SUBJ. #23)
(UNIT: PLASMA LEVEL=NG/ML TIME=HRS)(n=28)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	110.41	108.76	119.96	98.60	0.92
0.67	414.41	253.33	441.41	195.14	0.94
1	647.14	324.71	637.74	177.60	1.01
1.33	756.17	309.91	716.36	210.28	1.06
1.67	794.00	266.07	744.75	245.42	1.07
2	767.14	268.99	710.13	256.79	1.08
2.5	711.23	258.02	650.40	267.63	1.09
3	625.46	235.87	576.10	257.77	1.09
4	467.90	191.28	444.54	216.75	1.05
5	359.70	150.85	339.04	164.03	1.06
6	279.40	113.75	265.04	123.80	1.05
8	177.90	68.09	170.15	68.89	1.05
10	117.84	46.94	113.24	43.90	1.04
12	82.93	31.62	77.97	27.79	1.06
16	46.75	14.85	45.82	13.31	1.02
20	33.38	11.89	33.10	9.16	1.01
24	28.42	11.46	30.73	13.62	0.92

UNIT: PLASMA LEVEL=NG/ML TIME=HRS; 1=TEST, 2=REFERENCE

TABLE 2. ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	4870.93	1473.84	4713.91	1369.40	1.03
AUCT	4527.07	1462.80	4299.01	1425.05	1.05
CMAX	890.86	291.61	802.55	260.21	1.11
KE	0.09	0.03	0.09	0.03	1.06
LAUCI	4663.99	0.30	4523.98	0.30	1.03
LAUCT	4313.65	0.32	4084.14	0.33	1.06
LCMAX	854.60	0.28	761.28	0.34	1.12
THALF	8.09	2.97	9.14	4.22	0.89
TMAX	1.64	0.47	1.60	0.56	1.03

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR; 1=TEST, 2=REFERENCE

TABLE 3. LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	4870.93	4713.91	1.03	93.28	113.38
AUCT	4527.07	4299.01	1.05	93.36	117.25
CMAX	890.86	802.55	1.11	98.86	123.15
LAUCI	4663.99	4523.98	1.03	93.57	113.59
LAUCT	4313.65	4084.14	1.06	94.25	118.36
LCMAX	854.60	761.28	1.12	101.01	124.76

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR; 1=TEST, 2=REFERENCE

Deficiency 2. *Subject #23 in the study was dosed one week later. Although ANOVA analysis with or without Subject #23 does not affect the conclusions, the Agency discourages such replacements of subjects. Such replacements raise the issue of group effect, and create problems in statistical analysis.*

Response: The firm was attempting to keep the number to 30 as stated in the protocol. The replacement was made when Subject #23 withdrew from the study on personal grounds. No data analyses were made prior to the replacement.

Deficiency 3.

Response:

Conclusion: The explanation is acceptable.

Deficiency 4.

Response:

III. RECOMMENDATION

1. The *in vivo* bioequivalence study conducted under fasting conditions by Lederle on its Acyclovir Tablets, 800 mg strength, Lot #93264-0100, comparing it to Burroughs-Wellcome's 800 mg strength Zovirax^{R} Tablets, 800 mg strength, Lot #4M2463, has been found acceptable by the Division of Bioequivalence. The studies demonstrate that Lederle's 800 mg tablets, are bioequivalent to the Zovirax^{R} 800 mg tablets manufactured by Burroughs-Wellcome.

2. The firm has previously conducted an acceptable *in vivo* bioequivalence study under non-fasting conditions on its Acyclovir Tablets, 800 mg strength, Lot #93264-0100, comparing it to Burroughs-Wellcome's Zovirax^{R} Tablets, 800 mg strength, Lot #4M2463.

3. The firm has also conducted acceptable *in vitro* dissolution testing on its acyclovir 800 and 400 mg tablets. Lot #93264-0100 and Lot #93263-0100.

The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. and it should be conducted in 900 mL of water at 37 °C using USP 23 Apparatus 2 (Paddle) at 50 rpm. The test products should meet the following specifications:

Not less than , of the labeled amount of acyclovir in the dosage form is dissolved in 30 minutes.

4. From the bioequivalence point of view, the firm has met the *in vivo* bioavailability and *in vitro* dissolution testing requirements for its acyclovir 800 mg tablets, and the application is acceptable. The request for waiver of its acyclovir 400 mg tablets is granted.

The firm should be informed of the recommendations.

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED SNerurkar
FT INITIALED SNerurkar Date 4/23/97

Concur: Date: 4/23/97

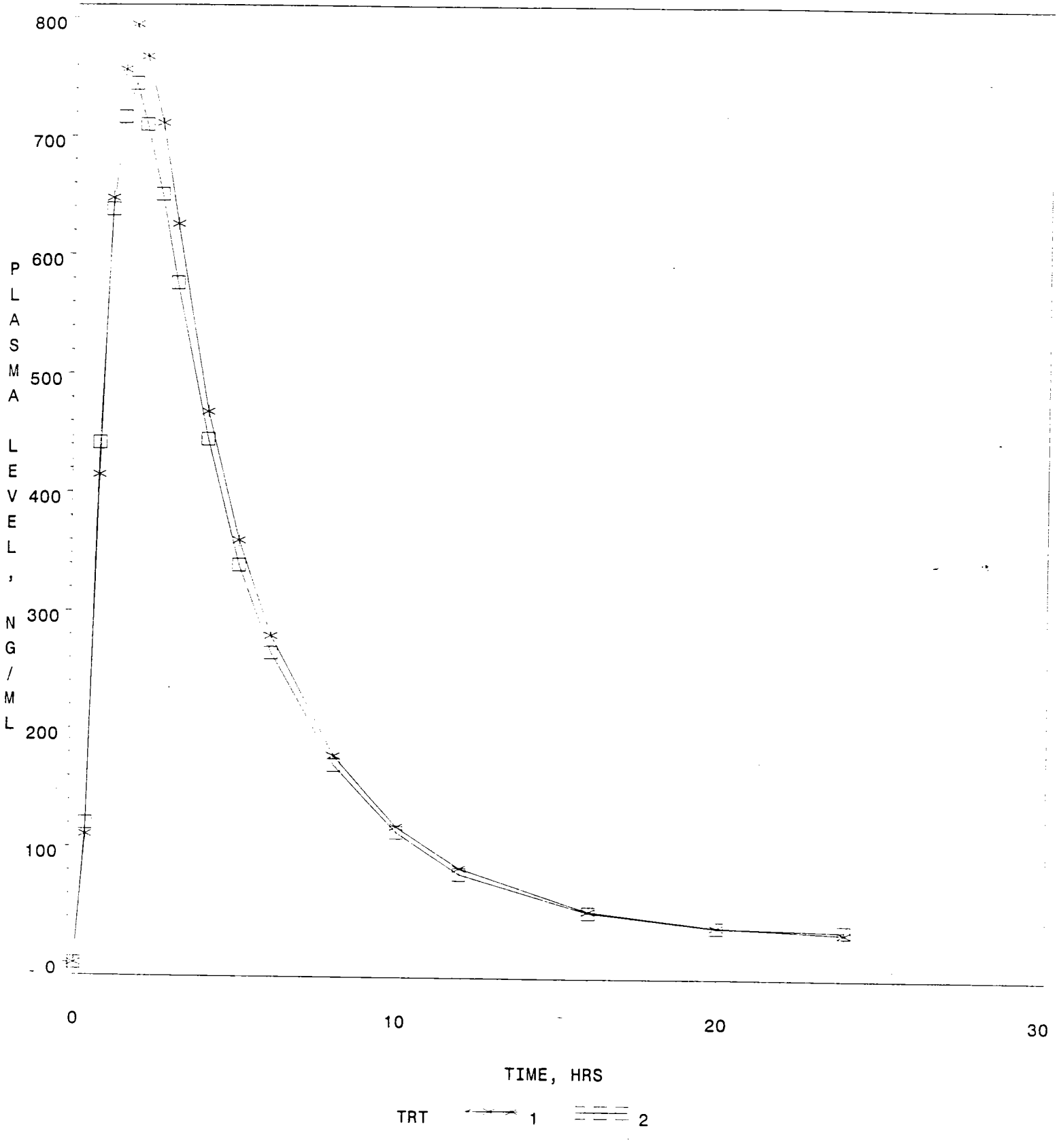
Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

Attachments-2
SPS/sps/4-4-97/74834o.n96

cc: ANDA #74834 (Original, Duplicate), HFD-655 (SNerurkar, SShrivastava), Drug File, Division File.

FIG P-1. PLASMA ACYCLOVIR LEVELS

ACYCLOVIR TABLETS, 800 MG, ANDA #74-834
UNDER FASTING CONDITIONS
DOSE=1 X 800 MG



DW

SEP 27 1996

Acyclovir Tablets
400 MG, 800 MG
ANDA #74-834
Reviewer: S.P. Shrivastava
WP #74834SDW.196

ESI-Lederle, Inc.
Pearl River, NY
Submitted:
January 12, 1996

REVIEW OF TWO BIOEQUIVALENCE STUDIES, DISSOLUTION DATA AND A WAIVER REQUEST

I. OBJECTIVES

Review of Lederle's two *in vivo* bioequivalence studies comparing its 800 mg strength Acyclovir Tablets to Burroughs-Wellcome's 800 mg strength Zovirax^{R} Tablets, under fasting and non-fasting conditions. The firm has also submitted *in vitro* dissolution data for review.

II. BACKGROUND

Acyclovir is 9-[(2-hydroxyethoxy)methyl]guanine, a synthetic purine nucleoside analog with *in vivo* and *in vitro* inhibitory activity against (in decreasing order) herpes simplex types 1 and 2 viruses, varicella zoster virus, Epstein-Barr virus, and cytomegalovirus. Acyclovir is converted by enzymes present in virus-infected cells into an active form, acyclovir triphosphate, which interrupts viral DNA replication. Acyclovir capsules and suspension are indicated for treatment of initial episodes and management of recurrent herpes simplex virus genitalis in certain patients. The capsule, suspension, and tablet dosage forms are indicated for treatment of acute herpes zoster and chicken pox.

Acyclovir oral absorption is slow, variable, and incomplete, with absolute bioavailability estimated at about 15-30%. Peak blood concentrations occur approximately 1.5-2.5 hours following oral dosing. There are no active metabolites. Studies in which 0.5 to 15 mg/kg were administered I.V. to patients with normal renal function yielded elimination half-lives of 2 to 3 hours. Renal excretion is the major route of elimination with 45-79% of a dose recovered unchanged in the urine.

Acyclovir is marketed as Zovirax (Burroughs-Wellcome) 200 mg capsules (NDA #18-828, 1/25/85), 800 mg and 400 mg tablets (NDA #20-089, 4/30/91), and oral suspension 200 mg/5 ml (NDA #19-909, 12/22/89).

III. SUMMARY OF BIOEQUIVALENCE STUDY PROTOCOLS

A. Single-Dose Fasting Study

1. Protocol # A419A-800

This randomized, single-dose, two-way crossover study was conducted with 30 healthy male volunteers in accordance with the Protocol. Subject #17 did not return for phase two of the study. Thus 29 subjects completed the study. In each period, subjects received a single 800 mg dose of either Lederle's acyclovir tablets or BW's Zovirax^{R} Tablets following an overnight

fast. There was a one-week wash-out period between treatments. Blood samples were collected pre-dose and for 24 hours after each dose. Plasma concentrations of acyclovir was measured by a Pharmacokinetic and statistical analyses were performed to compare the test and reference treatments.

2. Objective of the study

The objective of this study was to determine the bioequivalence of two acyclovir formulations after administration of single doses to healthy volunteers under fasting conditions.

3. Study design: Randomized, single-dose, two-way crossover study under fasting conditions.

4. Study sites Clinical study:
Analytical study:

5. Study dates:

Clinical study:	10/09/95-10/17/95 (All subjects Except Subject #23)
	10/16/95-10/24/95 (Make up group, Subject #23)
Analytical study:	10/18/95-11/27/95
Storage Time:	49 Days

6. Investigators: Principal Investigator -
Analytical Chemist -
Study Monitor -

A. Test: 800 mg Acyclovir Tablets (Lederle, Lot #93264-0100);
Exp. Date - 8/96; Lot Size - Potency - 99.5%.
B. Reference: 800 mg Zovirax^{R} Tablets (Burroughs Wellcome, Lot #4M2463);
Exp. Date 3/96; Potency - 101.4%.

7. Dosing: All doses were administered with 180 ml of water at room temperature, following an overnight fast.

8. Subjects: The 30 subjects who entered in this study were normal healthy male volunteers between the ages 19-35 years, and within 10% of their ideal weight as specified in the protocol. All subjects were selected based on the medical history, physical examination and clinical laboratory evaluations. Inclusion and exclusion criteria in the protocol were followed in the selection of the subjects.

Twenty-nine subjects completed both arms of the study. Subject #17 failed to return to Period II of the study. In addition, Subject #23 was dosed one week later. The reviewer analyzed the data with and without subject #23. The results showed that LC_{max} value failed the 90% CI criteria in both cases.

9. Food and fluid intake: Standard lunch was served 5 hours post-dose and dinner was served as scheduled on each day of drug administration. The drug products were administered with 180 mL of tap water. Water was allowed *ad lib.* except during one hour pre-dose and two hours post-dose period.

10. Washout period: One week.

11. Blood samples: In each period, 10 mL of blood samples were collected in Vacutainers at 0, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 hours. Plasma was separated and all plasma samples were stored frozen at -20°C until ready for analysis.

12. Subject safety monitoring: Subjects were asked to spontaneously report any signs or symptoms that might be related to the drug products.

13. Adverse reactions: On each dosing period subjects were asked to report any signs or symptoms judged to be drug related.

14. Pharmacokinetic and statistical analysis: Statistical analyses were performed on the pharmacokinetic parameters for acyclovir. 90% confidence intervals were calculated for AUC_{0-t}, AUC0-∞ and C_{max}.

B. Limited-Food Study

1. Protocol # A419B-800

2. Study design: Randomized, single-dose, three-way crossover study under fasting/non-fasting conditions.

3. Study Sites and Investigators: Same as in Fasting Study

4. Study dates:

Clinical study:	10/09 /95-10/24/95		
Analytical study:	11/06/95 - 11/22/95;	Storage Period:	43 Days

5. Treatments:

A. Test: 800 mg Acyclovir Tablets (Lederle, Lot #93264-0100) under non-fasting conditions.

B. Reference: 800 mg Zovirax^{R} Tablets (Burroughs Wellcome, Lot #4M2463) under non-fasting conditions.

C. Test: 800 mg Acyclovir Tablets (Lederle, Lot #93264-0100) under fasting conditions.

6. Dosing: All doses were administered with 180 mL of water at room temperature following an overnight fast or within 5 minutes after consuming the breakfast depending on the dosing schedule.

7. Subjects: Twenty subjects entered the study and 17 completed all three phases. Subjects #5, 12 (test-fast arm) and 13, were dropped due to positive urine drug screen at Period 2 check-in, Period 3 check-in, and at the beginning of the study, respectively. The subjects screened were normal healthy male volunteers aged 19-39 years, and were within 10% of their ideal body weight as specified in the protocol. All subjects were selected based on the medical history, physical examination and clinical laboratory evaluations. Inclusion and exclusion criteria in the protocol were followed in the selection of the subjects.

8. Food and fluid intake: Standard lunch and dinner were served on each day of drug administration. The drug products were administered with 180 mL of tap water. Water was allowed *ad lib.* except during one hour pre-dose and two hours post-dose period.

9. Wash-out period: One week.

10. Blood samples: Same as in the fasting study.

IV. VALIDATION OF ASSAY METHOD FOR PLASMA SAMPLES

V. RESULTS

A. Single-Dose Fasting Study

1. **Blood/Plasma Drug Concentration:** Since Subject #23 was dosed one week later, the subject should not belong to the same study period, and was excluded from the analyses. The mean plasma concentration data, with and without Subject #23, are given in Table 1 and 4 (pages 8-9), and graphic profiles are shown in Attachments 1 and 2, respectively.

2. **Pharmacokinetic Parameters**: Mean PK parameters and statistical analysis, with and without Subject #23 are given in Tables 2-3 and 5-6, respectively (pages 8-9). Individual data are shown in Attachments 3-4.

- The 90% CI for LAUCs are within 80-125% as required (Tables 3, 6). However, the LC_{max} does not meet the 90% CI criteria. LC_{max} is about 15% higher than the reference.

- Individual Test/Reference ratios for AUC_{0-t} ranged between with an average of 1.12 and CV of 36%.
- Individual Test/Reference ratios for AUC_{0-inf} ranged between with an average of 1.08 and CV of 30%.
- Individual Test/Reference ratios for C_{max} ranged between ith an average of 1.24 and CV of 42%.
- Individual Test/Reference ratios for T_{max} ranged between with an average of 1.64 and CV of 113%.
- The ratios of AUC_{0-t}/AUC_{0-inf} ranged between with an average of 0.92 and CV of 6%.
- Individual PK parameters and summary data are given in Attachments-3-4.
- Cmax value for Subject #28 given in table on page-166 should be 1406.4 ng/mL and not 661.1 ng/mL.

3. Adverse Reaction: No serious or unexpected adverse reactions were reported. The only event possibly related to the drug was headache in Subject #7 with reference drug.

Conclusion: The *in vivo* fasting study is not acceptable, because the test product does not meet the 90% CI criteria for LC_{max}.

TABLE 1. PLASMA CONCENTRATION OF ACYCLOVIR IN FASTING SUBJECTS (WITH SUBJ. #23)
(UNIT: PLASMA LEVEL=NG/ML TIME=HRS)
(n=29)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	109.12	107.02	115.83	99.35	0.94
0.67	415.46	248.83	429.57	201.95	0.97
1	643.73	319.39	629.91	179.43	1.02
1.33	750.25	305.99	715.09	206.60	1.05
1.67	790.86	261.82	748.44	241.82	1.06
2	800.20	285.59	710.12	252.16	1.13
2.5	711.86	253.39	652.78	263.12	1.09
3	624.32	231.70	579.42	253.75	1.08
4	467.61	187.84	445.68	212.93	1.05
5	359.82	148.13	340.97	161.40	1.06
6	279.15	111.71	266.88	121.97	1.05
8	177.31	66.94	171.08	67.83	1.04
10	117.26	46.21	113.87	43.24	1.03
12	82.24	31.27	78.53	27.46	1.05
16	46.17	14.91	46.06	13.14	1.00
20	32.98	11.88	33.12	9.00	1.00
24	27.96	11.52	30.52	13.42	0.92

1=TEST, 2=REFERENCE

TABLE 2. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION, WITH SUBJ. #23)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	4849.87	1451.72	4715.02	1344.74	1.03
AUCT	4513.35	1438.34	4306.80	1400.00	1.05
CMAX	915.28	298.39	804.25	255.68	1.14
KE	0.10	0.03	0.09	0.03	1.06
LAUCI	4649.45	0.30	4531.47	0.29	1.03
LAUCT	4307.15	0.31	4098.60	0.32	1.05
LCMAX	877.10	0.29	764.23	0.33	1.15
THALF	8.02	2.94	9.04	4.18	0.89
TMAX	1.65	0.46	1.60	0.55	1.03

1=TEST, 2=REFERENCE

TABLE 3. LSMEANS AND 90% CONFIDENCE INTERVALS (WITH SUBJ. #23)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	4843.52	4712.70	93.04	112.51
AUCT	4504.94	4304.95	93.09	116.20
CMAX	914.01	803.32	100.33	127.23
LAUCI	4645.55	4527.71	93.42	112.69
LAUCT	4300.78	4095.47	94.06	117.25
LCMAX	876.19	763.27	102.00	129.20

1=TEST, 2=REFERENCE

TABLE 4. MEAN PLASMA ACYCLOVIR LEVELS FOR TEST AND REFERENCE PRODUCTS (WITHOUT SUBJ. #23)
(UNIT: PLASMA LEVEL=NG/ML TIME=HRS)
(n=28)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	110.41	108.76	119.96	98.60	0.92
0.67	414.41	253.33	441.41	195.14	0.94
1	647.14	324.71	637.74	177.60	1.01
1.33	756.17	309.91	716.36	210.28	1.06
1.67	794.00	266.07	744.75	245.42	1.07
2	798.30	290.64	710.13	256.79	1.12
2.5	711.23	258.02	650.40	267.63	1.09
3	625.46	235.87	576.10	257.77	1.09
4	467.90	191.28	444.54	216.75	1.05
5	359.70	150.85	339.04	164.03	1.06
6	279.40	113.75	265.04	123.80	1.05
8	177.90	68.09	170.15	68.89	1.05
10	117.84	46.94	113.24	43.90	1.04
12	82.93	31.62	77.97	27.79	1.06
16	46.75	14.85	45.82	13.31	1.02
20	33.38	11.89	33.10	9.16	1.01
24	28.42	11.46	30.73	13.62	0.92

1=TEST, 2=REFERENCE

TABLE 5. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION, WITHOUT SUBJ. #23)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	4870.93	1473.84	4713.91	1369.40	1.03
AUCT	4527.07	1462.80	4299.01	1425.05	1.05
CMAX	917.48	303.62	802.55	260.21	1.14
KE	0.09	0.03	0.09	0.03	1.06
LAUCI	4663.99	0.30	4523.98	0.30	1.03
LAUCT	4313.65	0.32	4084.14	0.33	1.06
LCMAX	877.95	0.29	761.28	0.34	1.15
THALF	8.09	2.97	9.14	4.22	0.89
TMAX	1.64	0.47	1.60	0.56	1.03

1=TEST, 2=REFERENCE

TABLE 6. LSMEANS AND 90% CONFIDENCE INTERVALS (WITHOUT SUBJ. #23)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	4870.93	4713.91	93.28	113.38
AUCT	4527.07	4299.01	93.36	117.25
CMAX	917.48	802.55	100.38	128.26
LAUCI	4663.99	4523.98	93.57	113.59
LAUCT	4313.65	4084.14	94.25	118.36
LCMAX	877.95	761.28	102.04	130.34

1=TEST, 2=REFERENCE

B. Limited Food Study

A total of 20 subjects participated in the study and 17 completed the study successfully. Three subjects, Subjects #5, 12 and 13 were dropped-out, because they were positive in drug screen test. Two subjects, Subject #7 (test-fed) and Subject #1 (reference-fed) showed non-zero acyclovir levels at pre-dose sampling time. Because of this, the firm excluded these subjects from the analysis. No further explanation was given. This reviewer analyzed the data with Subjects #7 and 1 (Tables 7-12). The non-fasting study meets the BE criteria, with or without Subjects #7 and 1.

1. Blood/Plasma Drug Concentration

The average plasma concentration data, test/reference ratios, and plasma profiles are given in Tables 7-8 and Attachment-5. T/R (food) ratios during 1-24 hours are 0.91-1.07, and generally food increases the drug plasma concentration.

2. Pharmacokinetic Parameters

- Average pharmacokinetic parameters and test/reference (food) ratios are given in Tables 9-12.
- The ratios of average test/reference (food) for AUCs and C_{max} are within 0.8-1.2 as required (Tables 10).
- ANOVA analysis showed no significant period effect on AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max}.
- Individual PK parameters are given in Attachments 6-8.
- Food increases the C_{max}, T_{max} and AUCs, and it decreases T_{half}.

3. **Adverse Reaction**: No serious or unexpected adverse reactions were reported, and none appeared to be related to the study drug.

Conclusion: The non-fasting *in vivo* study is acceptable.

TABLE 7. MEAN PLASMA ACYCLOVIR LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS
(n=17)

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
TIME HR						
0	11.24	46.35	0.71	2.91	0.00	0.00
0.33	76.54	101.17	21.86	28.75	157.31	89.88
0.67	273.38	237.03	168.18	115.07	430.92	166.92
1	544.14	333.38	511.74	309.24	552.49	240.53
1.33	791.56	418.19	799.74	366.89	595.26	242.84
1.67	875.14	350.73	926.15	352.60	614.95	262.88
2	909.50	296.47	994.29	334.86	601.70	285.49
2.5	932.79	287.51	996.11	363.74	533.25	254.61
3	902.55	320.16	931.51	303.05	476.83	242.80
4	750.08	307.73	783.48	269.14	355.89	216.95
5	623.24	270.41	641.44	239.81	277.52	176.96
6	467.88	204.14	475.14	175.02	207.39	119.15
8	272.59	111.30	275.15	96.13	135.01	73.11
10	174.36	69.96	174.99	52.73	94.01	47.35
12	120.85	43.82	117.28	32.50	71.75	27.23
16	63.94	19.26	63.56	16.58	48.21	15.42
20	40.44	11.15	39.83	10.71	35.41	10.66
24	33.52	10.69	31.24	7.45	32.38	10.46

1=TEST FED, 2=REFERENCE FED, 3=TEST FASTING

TABLE 8. RATIO OF TEST/REFERENCE MEAN PLASMA ACYCLOVIR LEVELS
(UNIT: PLASMA LEVEL=NG/ML TIME=HRS)

	RMEAN12	RMEAN13	RMEAN23
TIME HR			
0	15.93	.	.
0.33	3.50	0.49	0.14
0.67	1.63	0.63	0.39
1	1.06	0.98	0.93
1.33	0.99	1.33	1.34
1.67	0.94	1.42	1.51
2	0.91	1.51	1.65
2.5	0.94	1.75	1.87
3	0.97	1.89	1.95
4	0.96	2.11	2.20
5	0.97	2.25	2.31
6	0.98	2.26	2.29
8	0.99	2.02	2.04
10	1.00	1.85	1.86
12	1.03	1.68	1.63
16	1.01	1.33	1.32
20	1.02	1.14	1.12
24	1.07	1.04	0.96

1=TEST FED, 2=REFERENCE FED, 3=TEST FASTING

TABLE 9. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)
(n=17)

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
PARAMETER						
AUCI	6574.58	1694.29	6591.55	1628.36	4446.31	1402.32
AUCT	6203.50	1744.00	6286.09	1661.32	3675.61	1449.51
CMAX	1132.07	318.55	1137.19	340.85	680.46	297.32
KE	0.11	0.04	0.11	0.02	0.07	0.03
LAUCI	6366.83	0.26	6391.54	0.26	4237.95	0.33
LAUCT	5971.11	0.29	6057.90	0.29	3416.41	0.40
LCMAX	1085.28	0.31	1084.50	0.33	610.65	0.51
THALF	7.27	2.56	6.64	1.78	11.09	5.46
TMAX	2.23	1.06	2.31	1.04	1.78	1.07

1=TEST FED, 2=REFERENCE FED, 3=TEST FASTING

TABLE 10. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	RMEAN12	RMEAN13	RMEAN23
PARAMETER			
AUCI	1.00	1.48	1.48
AUCT	0.99	1.69	1.71
CMAX	1.00	1.66	1.67
KE	0.97	1.44	1.49
LAUCI	1.00	1.50	1.51
LAUCT	0.99	1.75	1.77
LCMAX	1.00	1.78	1.78
THALF	1.09	0.66	0.60
TMAX	0.96	1.25	1.30

1=TEST FED, 2=REFERENCE FED, 3=TEST FASTING

TABLE 11. LSMEANS AND 90% CONFIDENCE INTERVALS
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	LSMEAN1	LSMEAN2	LSMEAN3	LOWCI12	UPPCI12	LOWCI13
PARAMETER						
AUCI	6576.79	6605.39	4060.80	88.48	110.65	143.93
AUCT	6193.64	6284.54	3647.66	88.23	108.88	152.01
CMAX	1130.94	1139.38	675.22	87.05	111.47	146.89
LAUCI	6387.66	6422.52	3960.50	87.47	113.08	141.85
LAUCT	5986.13	6076.34	3404.04	86.75	111.87	154.86
LCMAX	1093.90	1095.59	611.01	83.22	119.80	149.21

1=TEST FED, 2=REFERENCE FED, 3=TEST FASTING

TABLE 12. LSMEANS AND 90% CONFIDENCE INTERVALS
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	UPPCI13	LOWCI23	UPPCI23
PARAMETER			
AUCI	179.98	144.64	180.69
AUCT	187.59	154.50	190.08
CMAX	188.10	148.14	189.35
LAUCI	183.38	142.63	184.38
LAUCT	199.70	157.19	202.71
LCMAX	214.81	149.44	215.14

1=TEST FED, 2=REFERENCE FED, 3=TEST FASTING

VI. FORMULATION

Table 13. shows the composition of the test products, 400 mg and 800 mg Acyclovir Tablets by Lederle. The 400 mg and 800 mg strengths are exactly proportional in active and inactive ingredients.

The reference products contain same ingredients except for FD&C Blue No.2 and ferric oxide in 800 and 400 mg tablets, respectively.

[NOT FOR RELEASE UNDER F.O.I.]

Table 13. Composition of Lederle's Acyclovir Tablets

Ingredient	400 mg Test	400 mg Reference	800 mg Test	800 mg Reference
Acyclovir, USP	400.000	400.000	800.000	800.000
Povidone				
Microcrystalline Cellulose				
Sodium Starch Glycolate				
Magnesium Stearate				
Colloidal Silicon Dioxide				
Dye FDC Blue #2				
Ferric Oxide, Red				
Total Tablet Weight	525.000	521.500	1050.000	1044.000

VII. *IN VITRO* RESULTS (DISSOLUTION): Both, 400 and 800 mg tablets meet the dissolution requirement of Q=NLT in 30 minutes.

TABLE 14. *In Vitro* Dissolution Testing

A. Conditions

Method, Apparatus II (Paddle) **RPM: 50** **No. of Units: 12**
Medium: water **Volume:** 900 mL
Reference Drug: Zovirax® **Manufacturer:** Burroughs-Wellcome
Assay Methodology:

B. Results

Sampling Time (Minutes)	Test Product Mean % Dissol	Range	CV	Reference Product Mean % Dissol	Range	CV
	Lot #93263-0100		**Strength 400 mg**	**Lot # 4M2451**		
10	84		3.4	81		3.2
20	90		2.4	89		2.0
30	93		1.6	92		1.6
40	94		1.3	94		2.2
	Lot #93264-0100		**Strength 800 mg**	**Lot #4M2463**		
10	84		2.8	84		5.3
20	90		2.3	93		2.0
30	92		2.4	95		1.6
40	94		2.2	97		1.8

VIII. DEFICIENCIES

1. The product does not meet the 90% CI criteria for LC_{max} PK parameter. The LC_{max} of test product is 15% greater than the reference product.

2. Subject #23 in the study was dosed one week later. Although ANOVA analysis with or without Subject #23 does not affect the conclusions, the Agency discourages such replacements of subjects. Such replacements raise the issue of group effect, and create problems in statistical analysis.

3.

4. There is an error in reporting the C_{max} value of Subject #28 given in table on page-166. It should read 1406.4 ng/mL and <u>not</u> 661.1 ng/mL.

IX. RECOMMENDATION

1. The *in vivo* bioequivalence study conducted under fasting conditions by Lederle on its Acyclovir Tablets, 800 mg strength, Lot #93264-0100, comparing it to Burroughs-Wellcome's 800 mg strength Zovirax^R Tablets, 800 mg strength, Lot #4M2463, has been found unacceptable by the Division of Bioequivalence because of the deficiencies #1-3 cited above.

2. The *in vivo* bioequivalence study conducted under non-fasting conditions by Lederle on its Acyclovir Tablets, 800 mg strength, Lot #93264-0100, comparing it to Burroughs-Wellcome's Zovirax^R Tablets, 800 mg strength, Lot #4M2463, has been found acceptable by the Division of Bioequivalence.

3. The dissolution testing data conducted by ESI-Lederle, on its acyclovir 800 and 400 mg tablets, Lot #93264-0100 and Lot #93263-0100, are acceptable. The firm, however, has not conducted an acceptable *in vivo* bioequivalency study. Therefore, the application is incomplete.

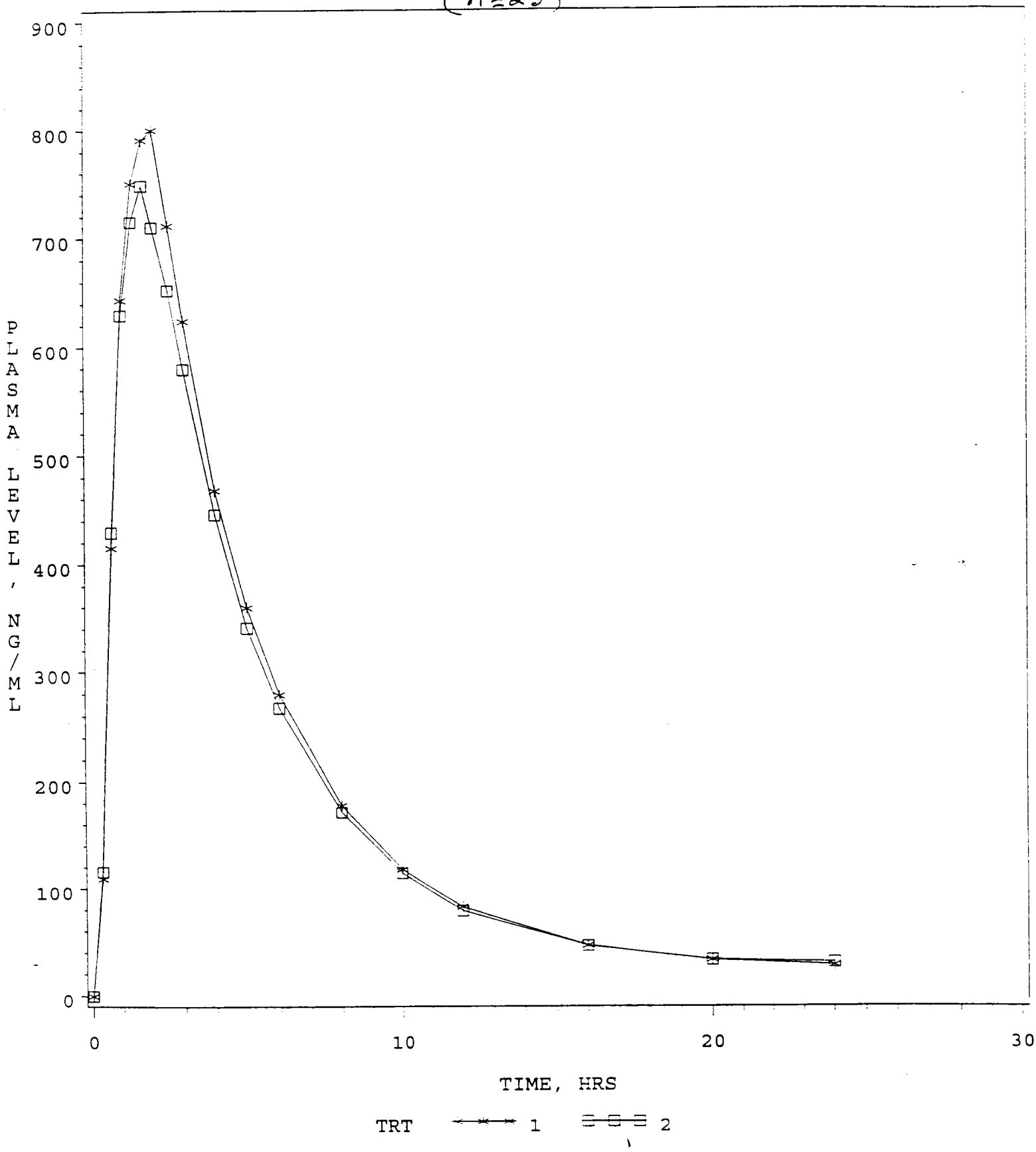
4. From the bioequivalence point of view, the firm has not met the *in vivo* bioavailability requirements for its acyclovir 800 mg tablets, and in the absence of an acceptable *in vivo* biostudy under fasting conditions, the request for waiver of its acyclovir 400 mg tablets cannot be granted. The waiver request is denied. The firm should resubmit the waiver request with a single-dose fasting study on 800 mg tablets.

The firm should be informed of the deficiencies #1-4 and recommendations #1 and 4.

Attachment - 1

FIG P-1. PLASMA ACYCLOVIR LEVELS

ACYCLOVIR TABLETS, 800 MG, ANDA #74-834
UNDER FASTING CONDITIONS
DOSE=1 X 800 MG
(n=29)

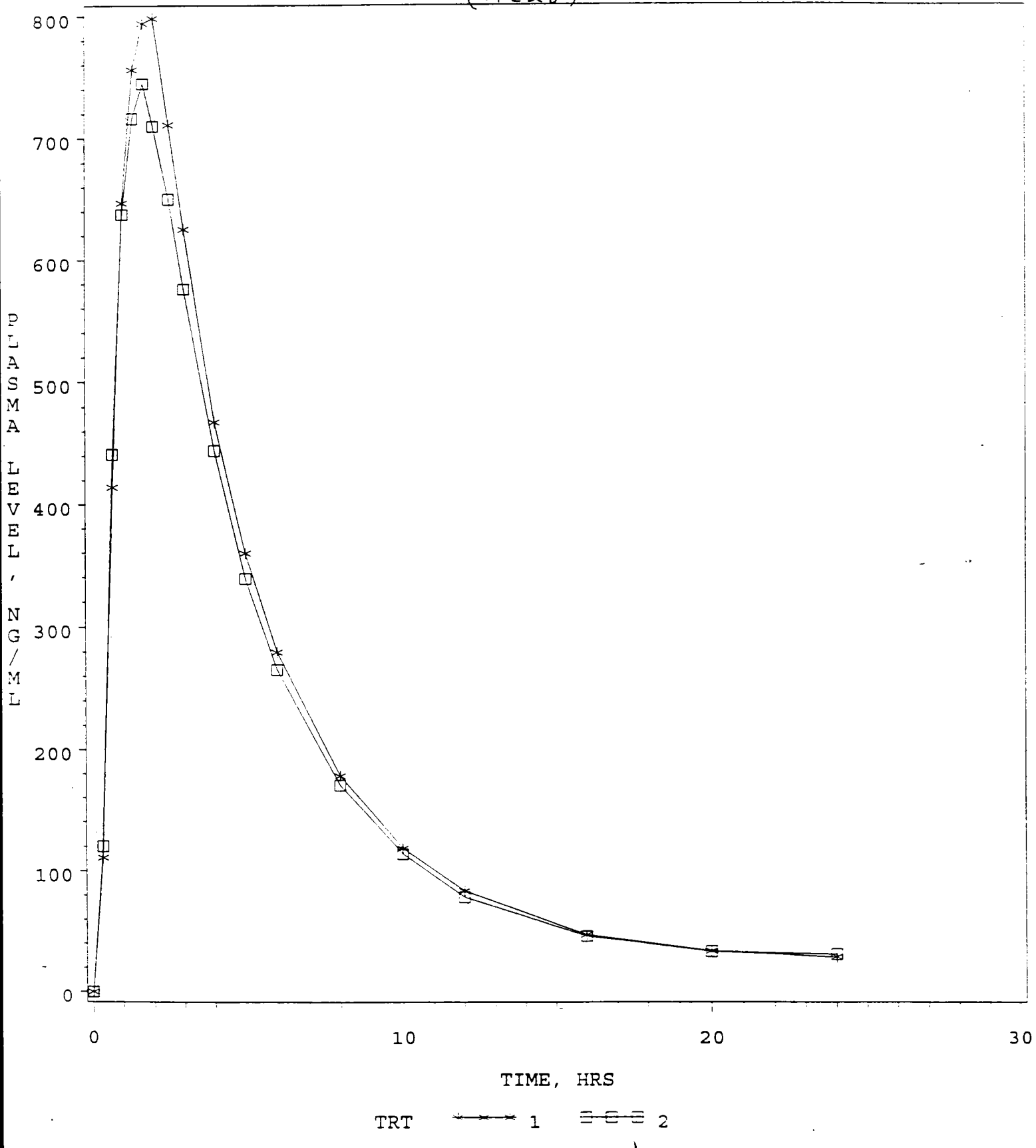


1=TEST PRODUCT(ESI-LEDERLE) 2=REFERENCE PRODUCT(BURROUGHS-WELLCOME)

Attachment - 2

FIG P-1. PLASMA ACYCLOVIR LEVELS

ACYCLOVIR TABLETS, 800 MG, ANDA #74-834
UNDER FASTING CONDITIONS
DOSE=1 X 800 MG
(n = 28)



1=TEST PRODUCT(ESI-LEDERLE) 2=REFERENCE PRODUCT(BURROUGHS-WELLCOME)

Lederle Pharmaceutical Division
Acyclovir Protocol A419A-800

Table # 15

Individual and Mean Pharmacokinetic Parameter Values From Plasma Acyclovir Concentrations for ESI Lederle Acyclovir 800 mg Tablet

Subject Number	Treatment Sequence	Study Period	Parameters: Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	Kel 1/hr	T 1/2el hr	Log-Parameters: LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
1	AB	1									
2	BA	2									
3	AB	1									
4	BA	2									
5	BA	2									
6	AB	1									
7	BA	2									
8	AB	1									
9	BA	2									
10	AB	1									
11	BA	2									
12	AB	1									
13	BA	2									
14	AB	1									
15	AB	1									
16	BA	2									
18	BA	2									
19	BA	2									
20	AB	1									
21	AB	1									
22	BA	2									
23	BA	2									
24	AB	1									
25	AB	1									
26	BA	2									
27	BA	2									
28	AB	1									
29	BA	2									
30	AB	1									
Mean			889.6	1.64	4500.8	4837.3	0.0953	8.02	6.751	8.364	8.441
S.D.			286.4	0.46	1449.5	1462.0	0.0278	2.94	0.277	0.314	0.299
C.V.(%)			32.2	28.01	32.2	30.2	29.1361	36.65	4.108	3.753	3.545
S.E.M.			53.2	0.09	269.2	271.5	0.0052	0.55	0.051	0.058	0.056
N			29.0	29.00	29.0	29.0	29.0000	29.00	29.000	29.000	29.000
Minimum			507.1	1.00	2208.8	2397.5	0.0384	4.31	6.229	7.700	7.782
Maximum			2030.6	3.00	8650.2	8939.9	0.1607	18.07	7.616	9.065	9.098

0166

Cmax for Subj. #28 is incorrect based on raw data on the disk and other tables. The correct value is 1406.4 ng/mL

7/3/96

Attachment - 5

Lederle Pharmaceutical Division
Acyclovir Protocol A419A-800

Table 8 16

Individual and Mean Pharmacokinetic Parameter Values From Plasma Acyclovir Concentrations
for Burroughs Wellcome Zovirax(R) 800 mg Tablet

Subject Number	Treatment Sequence	Study Period	Parameters: Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	Kel 1/hr	T 1/2el hr	Log-Parameters: LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
1	AB	2									
2	BA	1									
3	AB	2									
4	BA	1									
5	BA	1									
6	AB	2									
7	BA	1									
8	AB	2									
9	BA	1									
10	AB	2									
11	BA	1									
12	AB	2									
13	BA	1									
14	AB	2									
15	AB	2									
16	BA	1									
18	BA	1									
19	BA	1									
20	AB	2									
21	AB	2									
22	BA	1									
23	BA	1									
24	AB	2									
25	AB	2									
26	BA	1									
27	BA	1									
28	AB	2									
29	BA	1									
30	AB	2									
Mean			804.2	1.60	4306.5	4714.7	0.0898	9.04	6.639	8.318	8.419
S.D.			255.7	0.55	1400.0	1344.7	0.0333	4.18	0.331	0.321	0.290
C.V.(%)			31.8	34.32	32.5	28.5	37.0468	46.27	4.986	3.856	3.447
S.E.M.			47.5	0.10	260.0	249.7	0.0062	0.78	0.061	0.060	0.054
N			29.0	29.00	29.0	29.0	29.0000	29.00	29.000	29.000	29.000
Minimum			405.0	1.00	2123.2	2302.6	0.0303	4.00	6.004	7.661	7.742
Maximum			1366.6	3.00	7679.7	7765.6	0.1734	22.91	7.220	8.946	8.957

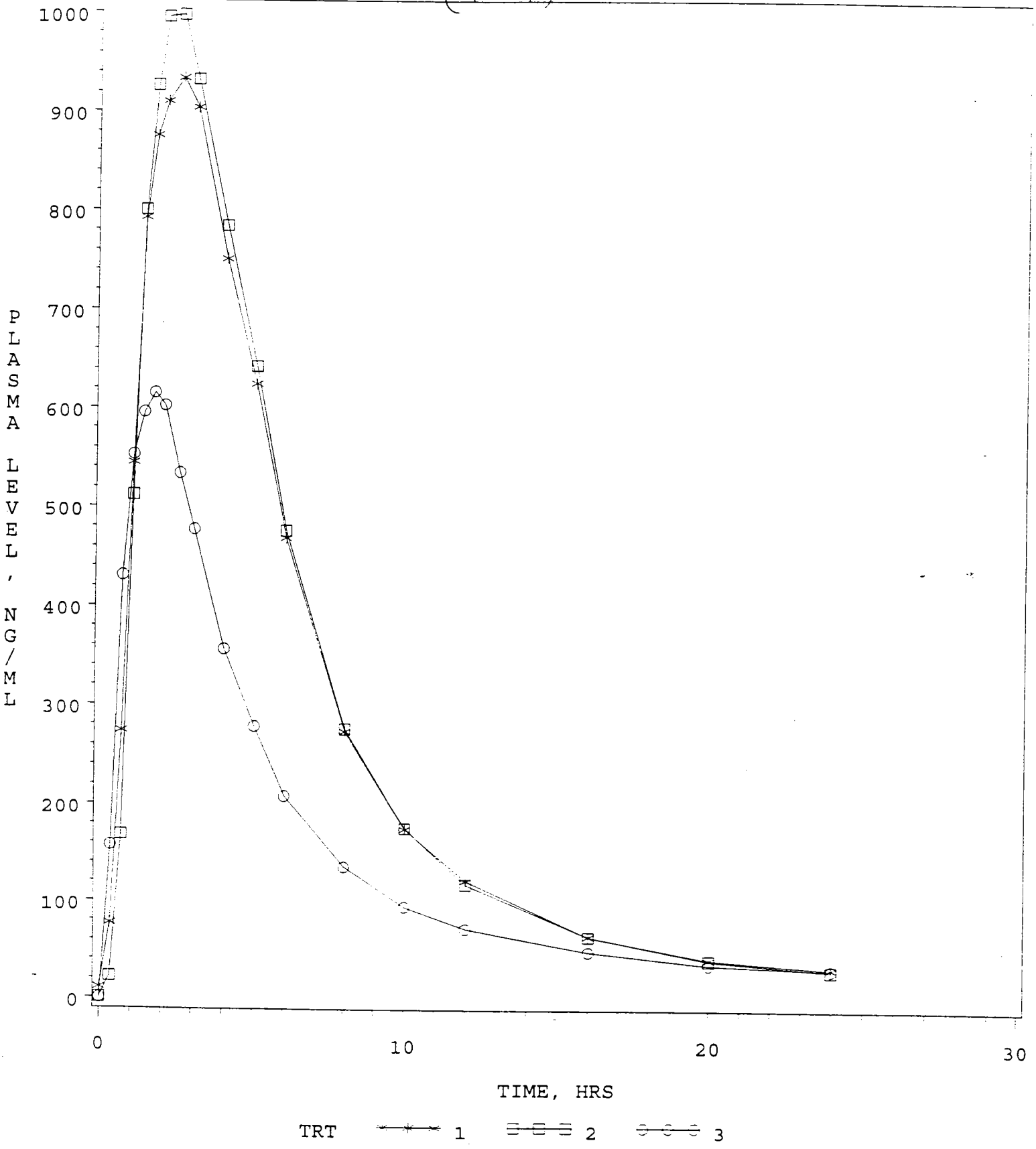
0167

Attachment 4

Attachment - 5

FIG P – 2. PLASMA ACYCLOVIR LEVELS

ACYCLOVIR TABLETS, 800 MG, ANDA #74-834
UNDER NON-FASTING CONDITIONS
DOSE=1 X 800 MG
(n = 17)



1=TEST FED (ESI-LEDERLE) 2=REFERENCE FED (BURROUGHS-WELLCOME) 3=TEST FASTING (ESI-LEDERLE)

Lederle Pharmaceutical Division
Acyclovir Protocol A419B-800

Table 17

Individual and Mean Pharmacokinetic Parameter Values From Plasma Acyclovir Concentrations
for ESI Lederle Acyclovir 800 mg Tablet (fed)

Subject Number	Treatment Sequence	Study Period	Parameters: Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	Kel 1/hr	T 1/2el hr	Log-Parameters: LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
1	CAB	2									
2	ACB	1									
3	BAC	2									
4	BCA	3									
6	ABC	1									
*7	CAB	2									
8	BCA	3									
9	CBA	3									
10	ABC	1									
11	ACB	1									
12	BAC	2									
14	ABC	1									
15	BAC	2									
16	CAB	2									
17	CBA	3									
18	BCA	3									
19	BCA	3									
20	ABC	1									
Mean			1125.0	2.18	6040.3	6405.7	0.1052	7.35	6.984	8.671	8.735
S.D.			316.56	1.07	1661.6	1616.2	0.0351	2.52	0.310	0.276	0.253
C.V.(%)			28.14	48.99	27.5	25.2	33.3581	34.31	4.434	3.178	2.892
S.E.M.			76.78	0.26	403.0	392.0	0.0085	0.61	0.075	0.067	0.061
N			17.00	17.00	17.0	17.0	17.0000	17.00	17.000	17.000	17.000
Minimum			503.90	1.00	3373.6	3820.1	0.0612	3.79	6.222	8.124	8.248
Maximum			1789.4	5.00	9571.2	9692.0	0.1831	11.32	7.490	9.167	9.179

Subject 7 data was excluded from summary statistics due to a pre-dose level

0559

Attachment - 6

Lederle Pharmaceutical Division
Acyclovir Protocol A419B-800

Table 18

Individual and Mean Pharmacokinetic Parameter Values From Plasma Acyclovir Concentrations
for Burroughs Wellcome Zovirax(R) 800 mg Tablet (fed)

Subject Number	Treatment Sequence	Study Period	Parameters: Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	Kel 1/hr	T 1/2el hr	Log-Parameters: LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
*1	CAB	3									
2	ACB	3									
3	BAC	1									
4	BCA	1									
6	ABC	2									
7	CAB	3									
8	BCA	1									
9	CBA	2									
10	ABC	2									
11	ACB	3									
12	BAC	1									
14	ABC	2									
15	BAC	1									
16	CAB	3									
17	CBA	2									
18	BCA	1									
19	BCA	1									
20	ABC	2									
Mean			1097.3	2.27	6078.8	6380.3	0.1089	6.78	6.961	8.676	8.731
S.D.			298.35	1.07	1641.3	1592.9	0.0262	1.91	0.305	0.288	0.257
C.V.(%)			27.19	46.92	27.0	25.0	24.0796	28.14	4.378	3.318	2.947
S.E.M.			72.36	0.26	398.1	386.3	0.0064	0.46	0.074	0.070	0.062
N			17.00	17.00	17.0	17.0	17.0000	17.00	17.000	17.000	17.000
Minimum			516.90	1.33	3182.1	3785.4	0.0605	4.27	6.248	8.065	8.239
Maximum			1711.4	5.00	9232.0	9522.8	0.1623	11.46	7.445	9.130	9.161

Subject 1 data was excluded from summary statistics due to a pre-dose level

0560

Attachment-7

Lederle Pharmaceutical Division
Acyclovir Protocol A419B-800

Table # 19

Individual and Mean Pharmacokinetic Parameter Values From Plasma Acyclovir Concentrations
for ESI Lederle Acyclovir 800 mg Tablet (fasted)

Subject Number	Treatment Sequence	Study Period	Parameters: Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	Kel 1/hr	T 1/2el hr	Log-Parameters: LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
1	CAB	1									
2	ACB	2									
3	BAC	3									
4	BCA	2									
6	ABC	3									
7	CAB	1									
8	BCA	2									
9	CBA	1									
10	ABC	3									
11	ACB	2									
*12	BAC	3									
14	ABC	3									
15	BAC	3									
16	CAB	1									
17	CBA	1									
18	BCA	2									
19	BCA	2									
20	ABC	3									
Mean			680.46	1.78	3675.6	4446.3	0.0739	11.09	6.415	8.136	8.352
S.D.			297.32	1.07	1449.5	1402.3	0.0275	5.46	0.510	0.399	0.329
C.V.(%)			43.69	59.79	39.4	31.5	37.1887	49.22	7.950	4.905	3.935
S.E.M.			72.11	0.26	351.6	374.8	0.0073	1.46	0.124	0.097	0.088
N			17.00	17.00	17.0	14.0	14.0000	14.00	17.000	17.000	14.000
Minimum			230.30	0.67	1739.9	2140.2	0.0275	5.72	5.439	7.462	7.669
Maximum			1280.1	5.00	7158.1	7575.9	0.1212	25.21	7.155	8.876	8.933

Subject 12 data was excluded from summary statistics because the subject did not complete this study period

0561

Attachment - 8